Neuroimaging in Traumatic Brain Imaging

Bruce Lee* and Andrew Newberg[†]

Department of Medicine, [†]Division of Nuclear Medicine, Department of Radiology, University of Pennsylvania Health System, Philadelphia, Pennsylvania 19104

Summary: Traumatic brain injury (TBI) is a common and potentially devastating clinical problem. Because prompt proper management of TBI sequelae can significantly alter the clinical course especially within 48 h of the injury, neuroimaging techniques have become an important part of the diagnostic work up of such patients. In the acute setting, these imaging studies can determine the presence and extent of injury and guide surgical planning and minimally invasive interventions. Neuroimaging also can be important in the chronic therapy of TBI, identifying chronic sequelae, determining prognosis, and guiding rehabilitation. **Key Words:** Head injury, MRI, PET, neuroimaging, trauma, SPECT, CT.

INTRODUCTION

Traumatic brain injury (TBI) is an extremely common and potentially devastating problem. Studies have estimated that nearly 1.6 million head injuries occur in the United States each year, resulting in over 50,000 deaths and over 70,000 patients with permanent neurological deficits.[1–3] TBI accounts for up to 10% of the health care budget and an estimated annual cost to society of $30 billion.[4] Because prompt proper management of TBI sequelae can significantly alter their course especially within 48 h of the injury, neuroimaging techniques, which can determine the presence and extent of the injury and guide surgical planning and minimally invasive interventions, play important roles in the acute therapy of TBI.[4] Imaging also can be important in the chronic therapy of TBI, identifying chronic sequelae, determining prognosis, and guiding rehabilitation.

The following review will discuss the indications for imaging patients with TBI, review the roles of x-ray computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), and angiography in the management of TBI, and discuss potential future applications of these imaging modalities.

The reader is referred to a separate review on imaging of animal models of TBI published in the current volume.[5]

INDICATIONS FOR IMAGING

Not all head trauma patients require neuroimaging.[6] Neuroimaging is, of course, costly and can consume scanner time that may be used for patients with other indications. Studies have found that less than 10% of patients that are considered to have minor head injuries have positive findings on CT and less than 1% require neurosurgical intervention.[7] But this implies that there are still a small number of low risk patients that would benefit from neuroimaging. On the other hand, reducing the number of CT's performed on minor head injury patients even by 10% may yield more than $10 million in savings each year.[8,9]

Defining minor *versus* major head injuries has been problematic. Certain circumstances suggest major injury and almost always merit imaging such as worsening level of consciousness, loss of consciousness for more than 5 min, focal neurological findings, seizure, failure of the mental status to improve over time, penetrating skull injuries, signs of a basal or depressed skull fracture, or confusion or aggression on examination.[7,10–16] However, there is debate over which other circumstances merit imaging. Whereas numerous criteria have been developed, including the New Orleans Criteria[17] and the Canadian Head CT rules,[18,19] none have been found to be completely foolproof. Even patients with the complete absence of clinical findings and high risk circumstances

Address correspondence and reprint requests to Andrew B. Newberg, M.D., Division of Nuclear Medicine, 110 Donner Building, H.U.P., 3400 Spruce Street, Philadelphia, PA 19104. E-mail: newberg@rad.upenn.edu.

have been found to have intracerebral hemorrhage on imaging.[20] Nevertheless, most investigators have focused on several criteria:

Glasgow coma scale

The Glasgow Coma Scale (GCS), which rates a patient's level of consciousness from 3 (worst) to 15 (no impairment) based on a patient's ability to open his or her eyes, talk, and move, is often used to assess injury severity. Some have suggested that any score below 15 warrants imaging,[21,22] whereas other investigators have suggested that imaging should not be performed unless the score is below 13.[23–25]

Vomiting and headache

Based on the New Orleans Criteria, all TBI patients with headache or vomiting should be imaged. More than two episodes of vomiting is considered by Canadian CT head rules as a high-risk factor for requiring neurosurgical intervention.[18,19] However, a meta-analysis found that the presence of headache or vomiting were not predictive of intracranial hemorrhage in the pediatric population.[26]

Amnesia

While amnesia is included in both the New Orleans criteria[17] and Canadian CT head rules,[18,19] transient amnesia is common after mild head injury. Thus, longer and more severe amnesic episodes imply a greater chance of hemorrhage. A SPECT study found that amnesia lasting more than half an hour is associated with bilateral cerebral hypoperfusion.[27]

Ethanol or drug intoxication

The New Orleans criteria list intoxication as an indication for imaging. Series have found that up to 8% of ethanol intoxicated patients had intracerebral injury.[6,28] Several mechanisms have been proposed. First of all, intoxicated patients with impaired sensoria and judgment may be more likely to suffer severe mechanisms of injuries. Secondly, chronic abuse has been found to cause brain atrophy, perhaps making the brain susceptible to insult. Finally, the presence of alcohol or other drugs of abuse may potentiate the effect of TBI on neurons and vasculature.[29]

Age (>60 years and infants)

According to the New Orleans criteria, all head injury patients over 60 years of age should undergo imaging,[17] and according to the Canadian CT head rules, anyone over 65 years of age is at high risk for needing neurosurgical intervention.[18,19] Studies have also shown a high incidence of intracranial injuries among infants who had no signs or symptoms, suggesting that imaging should be pursued more aggressively in younger children.[30–33]

Anticoagulation or coagulopathies. Although one study showed that patients with abnormal clotting studies were more likely to have delayed brain injury on CT,[34] it has not been clearly established if anticoagulation or coagulopathies should affect the decision to image.[28]

IMAGING AND ACUTE MANAGEMENT

In the acute setting, early diagnosis and aggressive management may prevent secondary injury from the complications of brain injury. Proper management can significantly improve mortality and morbidity, while reducing hospital stay and health care costs.[35,36] Imaging helps identify cerebral and cranial problems and determine their severity and operability, especially when reliable, complete neurological examinations cannot be performed. Imaging has become essential to surgical planning by providing anatomic localization and navigation information, determining extracranial landmarks to help plan the skin incision, and guiding placement of burr holes when necessary. Imaging findings also can provide important prognostic indicators, which may help decide the aggressiveness of management.[37–39]

Anatomical imaging with MRI is very sensitive and accurate in diagnosing cerebral pathology in TBI patients. However, conventional CT (which is more available and cost effective, requires shorter imaging time and is easier to perform on patients who are on ventilator support, in traction, or agitated) is the initial imaging modality of choice during the first 24 h after the injury.[8,40–42] The advent of fast multidetector CT has dramatically reduced scanning time and allows for quick selective rescanning of slices that are affected by motion artifact.[43] CT is also superior in evaluating bones and detecting acute subarachnoid or acute parenchymal hemorrhage.[44]

Conventional CT also has its limitations. Beam-hardening effects, displacement of the CT signal near metal objects, bone, calcifications, and high concentrations of contrast, can degrade the image quality and prevent accurate assessment. CT can miss small amounts of blood that occupy widths less than a slice because of volume averaging. CT findings may lag behind actual intracranial damage, so that examinations performed within 3 h of trauma may underestimate injury.[45] In the absence of changes in neurological status, it is still under debate whether CT scans should be repeated after a normal admission CT.[46–48]

Forty-eight to 72 h after injury, MRI is generally considered to be superior to CT. Although CT is better at detecting bony pathology and certain types of early bleeds, the ability of MRI to detect hematomas improves over time as the composition of the blood changes. The overwhelming majority of patients with mild brain injury show no abnormality on MRI. When abnormalities are present, the most common findings are hemorrhagic cortical contusions, petechia, or foci of altered signal that
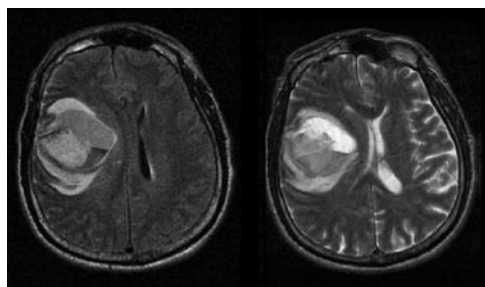
FIG. 1. MRI of 66-year-old male after a motor vehicle accident showing a large right frontal intraparenchymal hemorrhage on the FLAIR (left image) and T2 (right image) sequences. The FLARE images shows diffuse, heterogeneous increased signal intensity consistent with evolving blood products with surrounding edema in the frontal lobe.

represent white matter shear injury. When petechia resolve, they leave a permanent hemosiderin deposition on MRI. MRI is superior to CT in detecting axonal injury, small areas of contusion, and subtle neuronal damage.[49,50] Studies have shown that CT missed approximately 10–20% of abnormalities seen on MRI.[51,52] Moreover, MRI is better at imaging the brainstem, basal ganglia, and thalami. However, although the greater sensitivity of MRI is helpful in the subacute and chronic settings, it has not been established whether finding the additional lesions that MRI can detect would significantly change acute management of head trauma.[44,50,53] Moreover, white matter changes can be found in a large percentage of healthy middle-aged individuals.

New MRI technology and acquisition sequences have improved the sensitivity of MRI. Ashikaga and colleagues[54] found fluid-attenuated inversion recovery (FLAIR) MRI, a sequence that suppresses the high signal from CSF by using a long inversion time (T1), to be more sensitive in detecting traumatic lesions and hematomas (FIG. 1). McGowan and colleagues[55] demonstrated that magnetization transfer imaging (MTI), which applies radio frequency power only to the protons in the macromolecules of tissues rather than the protons in water, can add sensitivity to MRI. In a study by Lewine and colleagues,[56] magnetic source imaging, using a combination of MRI and magnetoencephalography, was superior to MRI alone. In separate studies, Sinson and colleagues and Cecil and colleagues[57,58] found proton magnetic resonance spectroscopy to be a sensitive tool in detecting axonal injury in the corpus callosum of TBI patients. Functional MRI can demonstrate changes in regional brain activation in patients with mild TBI.[59] However, all of these techniques still fell far short of 100% sensitivity in most studies reported in the literature. Moreover, they are not routinely available in many medical centers, and while the improved sensitivity may allow better prediction of outcomes, future studies will be necessary to determine how these improvements may impact acute management of TBI.

Currently, the advantages of cost and convenience for CT have limited the use of MRI in the acute management of TBI. As MRI becomes more available, newer sequences provide more information, and scanning time decreases, this may change.[5] Moreover, the development of shorter MR studies using fast pulse sequences on ultra low, low, or intermediate field strength systems and nonferromagnetic monitoring and ventilation devices may allow more patients to be scanned. Additionally, investigators are using MRI to better understand the mechanisms of secondary injury in brain trauma. This may lead to preventative or preemptive treatments in the acute setting. Eventually, MRI may become a more useful tool for the early evaluation of acute brain injury.

Neither PET nor SPECT imaging is used routinely in the acute management of head trauma. Both have limited availability especially during off-hours and require a fair amount of time to complete. Because PET and SPECT imaging provide functional rather than detailed anatomic information, neither is likely to replace CT or MRI in the acute setting of head trauma. In addition, it is always important to use PET and SPECT in conjunction with anatomical imaging. Currently, SPECT and PET are more useful in guiding long-term therapy by helping establish a patient's prognosis.

Hemorrhage and edema

Hemorrhage or edema can cause mass effect, which can directly compress vascular structures, resulting in ischemia and infarct, directly impinge upon other vital structures, or herniate different parts of the brain. Therefore, hemorrhage or edema that is either worsening or already large enough to produce mass effect should be urgently evacuated. Imaging plays a crucial role in identifying, following, and governing management of these conditions. Because hemorrhages frequently progress and large contusions often develop delayed hemorrhage or edema, repeat imaging is usually indicated, especially if changes in neurological status occur. The location of the bleed helps determine the risk of mass effect and management. It also affects the relative accuracy of CT and MRI.

Brain contusions are relatively common, occurring in up to 43% of patients with blunt trauma and frequently as coup or contrecoup injuries in deceleration or acceleration trauma.[60] Contusions associated with a fall, anisocoria, low GCS scores, or older patients (>60) are likely to benefit from prompt neurosurgical intervention.[61] On noncontrast CT, contusions appear as low attenuation if hemorrhage is absent and mixed or high attenuation if hemorrhage is present. In the acute stage, CT is more sensitive than MRI, as the clot signal can be indistinguishable from brain parenchyma on MRI. After the first few hours, the hemoglobin in the contusion loses its oxygen to become deoxyhemoglobin, which is still not

FIG. 2. CT of an 87-year-old female status post fall showing a large subdural hematoma along the left cerebral convexity with significant midline shift and effacement of the left lateral ventricle.

FIG. 3. CT of an 80-year-old female status post fall showing a large left subdural hematoma in addition to substantial subarachnoid hemorrhage (arrows).

well visualized on T1-weighted MRI, but the concentration of red blood cells and fibrin can cause low signal on T2-weighted images. Over the next several days, as the contusion liquefies and the deoxyhemoglobin oxidizes to methemoglobin that is strongly paramagnetic, the contusion becomes more easily visualized on MRI.[62]

Subdural hematomas (FIG. 2) are also relatively common (10–20% of patients with head trauma) and are associated with high mortality (50–85%).[61] The proximity of the skull can create beam hardening effects and also cause small hematomas to spread in a convex manner making volume averaging problems more likely. Using subdural CT windows (i.e., wider soft tissue windows) can compensate for this problem. In the subacute stage, after the initial several days, subdural hematomas approach the attenuation of normal brain parenchyma and MRI becomes more effective than CT in detection.[63]

Subarachnoid hemorrhages (SAH; FIG. 3) are more common in children and the elderly, who have relatively large subarachnoid spaces, and occur in up to 11% of TBI patients. It is often seen adjacent to a contusion. CT is superior to conventional MRI sequences in detecting acute SAH because the blood in acute SAH has a low hematocrit and low deoxyhemoglobin, which makes it appear similar to brain parenchyma on T1- and T2-weighted spin echo images. However, FLAIR sequences may find small acute or subacute SAH missed by CT and conventional MRI.[54,63,64]

Epidural hematomas are relatively uncommon (1–4% of head trauma patients) and are often associated with skull fractures. No intervention is required in stable epidural hematomas that are less than 1.5 cm in maximum

width, asymptomatic, located along the convexities, and produce minimal midline shift.

Whereas intraventricular hemorrhages are also uncommon (2.8%), they can be associated with significant morbidity and mortality. In one series, nearly half of patients with intraventricular hemorrhage developed elevated increase intracranial pressure, and 10% required ventricular drainage. On noncontrast CT, blood is of higher attenuation than the low attenuation CSF. CSF can confound interpretation on conventional MRI sequences. CSF pulsation artifacts may be misinterpreted as intraventricular hemorrhage. However, studies have suggested that FLAIR and fast spin echo FLAIR MRI may be superior to noncontrast CT.[63]

Increased intracranial pressure

Increased increased intracranial pressure (ICP) may require ICP monitoring and treatment by osmotic agents, drainage, or hyperventilation. The absence of findings on CT certainly does not exclude elevated ICP, but the presence of any of the following should raise suspicion for intracranial hypertension: loss of gray-white junction which indicates cerebral edema, midline shift, a hematoma mass, subdural hematoma, herniation, or change in ventricular shape or size. Miller and colleagues[65] found a linear association between ICP and CT findings. CT also can guide percutaneous placement of ICP monitors.[66]

Cerebral herniation

Cerebral herniation is a potentially devastating occurrence that can lead to compression of vital structures, vasculature, and cranial nerves. Although herniation most frequently occurs in the setting of diffuse cerebral edema, it
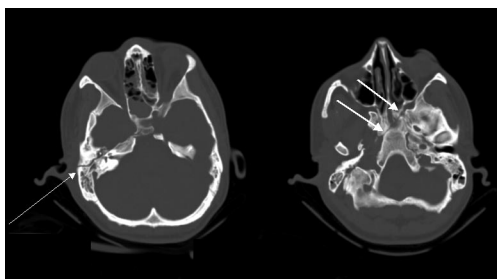
FIG. 4. CT scan of 35-year-old male with recent motor vehicle accident demonstrating longitudinal fracture of the right petrous bone (thin arrow) that extends into the skull base (thick arrow).

can occur with normal ICP when a small volume clot involves the border of two intracranial components.[67]

CT and MRI can effectively diagnose cerebral herniation. However, in some cases, MRI may be superior. The better soft tissue definition of MRI and its multiplanar imaging ability are particularly important in descending transtentorial herniation (caudal decent of the brain through the tentorial incisura).[67-69] Moreover, beam hardening artifacts from the skull base and partial volume averaging effects can interfere with CT interpretation of tonsilar herniations (inferior displacement of the cerebral tonsils through the foramen magnum into the cervical spinal canal).[67,70] Efforts have been made to correlate quantitative measures of herniation on imaging (i.e., the degree of shift of structures) with clinical outcomes. For example, in subfalcine herniation (midline shift or cingulated herniation), the degree of displacement of the septum pellucidum from the midline is predictive of patient prognosis. In studies of descending transtentorial herniation, the degree of vertical descent did not always correlate well with neurological signs. Because quantitative measures may be cumbersome and not be practical in clinical settings, qualitative measures may be adequate in governing management.[67,69,71,72]

Fractures

Depending on the location, size, and type of fracture, fractures may need to be surgically repaired to relieve or prevent CSF leakage, infection, hemorrhage, or vascular compromise. Although plain films of the skull may detect fractures, CT is the imaging modality of choice (FIG. 4). Open skull fractures depressed more then the full thickness of the skull should be surgically elevated.[73] Fractures involving the paranasal sinuses, mastoid air cells, or the entire thickness of the calvarium can allow air to enter the intracranial space. Such pneumocephalus is often absorbed over time, but when persistent, raises suspicion of a CSF lead. Patients with basilar skull fractures should receive a follow-up CT scan to exclude pneumocephalus. Air appears as an area of low attenuation on CT and signal void on MRI.[74]

Several imaging modalities have been used to identify CSF leaks: radionuclide with 111-Indium or 99m-Tc

DTPA, CT cisternography, and MRI using a three-dimensional-constructive interference steady-state sequence. Whereas radionuclide studies are sensitive for detecting the presence of CSF leaks, alone they are poor at providing precise anatomic localization, which is needed to guide surgical repair. Radionuclide cisternography and contrast-enhanced CT cisternography have been traditionally used. Studies have suggested that high-definition CT alone may be adequate at detecting small fractures that are the sites of CSF leaks, while sparing patients the discomfort of an intrathecal injection and nasal pledgets.[75,76]

Foreign bodies

With the rising prevalence of firearms injuries, it is increasingly common to find foreign bodies in the head. Depending on their size and velocity, foreign bodies can cause damage by several mechanisms: direct laceration, shock-wave transmission (pulsations that emanate from the front of a projectile), and cavitation (the motion of the foreign body creates a suction force in its path).[77] In addition to finding foreign objects and determining if removal is necessary, imaging can help track the path and subsequent movement of the foreign body and anticipate the corresponding complications. Non-contrast CT remains the imaging modality of choice. Because metallic objects can cause significant streak artifacts, if necessary and possible, reimaging the patient while angling the gantry to avoid the metallic object can alleviate this problem. Studies on the use of MRI have been limited and have not found MRI to add information to affect acute management. Moreover, although many commercial bullets are nonferromagnetic, if there is a chance that ferromagnetic metal is present, MRI should not be used.[77]

Vascular injury

Trauma can disrupt arterial walls and lead to dissections, aneurysms, or fistulae. The actual incidence of vascular damage in head trauma is unclear because many lesions are asymptomatic and nowadays angiography is only performed when damage is suspected. Imaging is used to identify the presence of the vascular lesion, inform the decision to repair by determining lesion size, location, and collaterals, and guide the type and approach of the intervention.

Although contrast angiography has been the gold standard for diagnosis of vascular lesions, MRI, MRA, and CT angiography (CTA) are growing in use and capability.[78] Unlike conventional angiography that only images the lumen of blood vessels, MRA and CTA can provide information about the arterial walls and MRI about the adjoining brain parenchyma.[78] CTA offers better resolution and fewer flow-related artifacts than MRA.[79-81]

Treatment of vascular lesions can be via either open surgical or endovascular approaches. Imaging can delin-

eate anatomy and guide open surgical approaches.[82,83] Adjoining injury can block or hinder open surgical approaches. Therefore, endovascular repair, which is also less invasive, is frequently preferable. Dissections, aneurysms, and fistulae may be treated with endovascular coil embolization or stent-grafts. When the affected vessel cannot be treated, the parent artery may need to be occluded.[84–86]

Cerebral ischemia

Almost all of the complications of head trauma can lead ultimately to cerebral ischemia, which if untreated can result in significant morbidity and mortality. Sometimes head trauma complications are not readily identifiable, and decreased cerebral perfusion is the only sign that a correctable problem exists. Cerebral ischemia can occur in the absence of CT findings or before CT findings evolve. Because conventional CT is poor at detecting cerebral ischemia, investigators have explored the use of other modalities to detect alterations in cerebral perfusion.[78,87]

Perfusion CT, currently used in acute stroke and other cerebrovascular disorders, may have a role in the routine evaluation of head trauma patients. In perfusion CT, nonionic iodinated contrast material is administered intravenously, and multiple sequential CT images of the head track the flow of contrast material through the brain.[78] Comparisons with stable xenon CT and PET have found that perfusion CT accurately assesses brain perfusion.[88,89] Wintermark and colleagues[90] found perfusion CT to be more sensitive (87.5% *vs* 39.6%) than conventional noncontrast CT in detecting cerebral contusions. They also found abnormalities on perfusion CT to correlate with unfavorable clinical outcomes.

However, cerebral perfusion can be difficult to interpret in the acute phase when cerebral blood flow is uncoupled from metabolism. Injured areas may be hypo-, iso-, or hyperperfused. Hyperemia can be global, which has been linked with increased intracranial pressure, deep coma, and poor prognosis, or focal, which may or may not be associated with lower mortality.[91] Furthermore, the perfusion abnormalities may result from primary vascular problems or from neuronal dysfunction and these two etiologies may be difficult to distinguish using functional imaging studies.

IMAGING AND CHRONIC MANAGEMENT

In the chronic management of head trauma, imaging has several potential roles: identifying postoperative neurophysiologic sequelae, evaluating the underlying functional abnormalities associated with late complications of head trauma, predicting long-term prognosis, guiding rehabilitation, and developing new therapies to prevent secondary injury. TBI patients can suffer from a wide variety of physical, emotional, psychological, and social difficulties that require multi-disciplinary therapy.[92–94] In fact, TBI patients may be unaware that specific neurological deficits may be causing problems.[95]

Chronic and delayed hemorrhage

Hemorrhage can start or continue beyond the initial few days after trauma. Reaccumulation of blood may occur after evacuation, which can be best detected by CT. CT can detect other postoperative complications as well, such as subdural empyema, brain abscess, brain stem hemorrhage, cerebral edema, tension pneumocephalus, and intracerebral hemorrhage. CT is also the imaging modality of choice in revealing delayed cerebral hematoma, which should be suspected in anyone who exhibits worsening level of consciousness, new third nerve palsy, or increasing ICP, can detect delayed extra-axial hematomas, but may miss small subdural hematomas caught by MRI.[74,96]

As time progresses, hematomas decrease in attenuation until they becomes isodense with normal brain parenchyma 3–10 weeks after the bleed, making it difficult to detect on CT.[97,98] Because old blood still emits high signal intensity on T1-weighted imaging, MRI is better at detecting chronic hemorrhage.[99,100] Chronic subdural hematomas rarely spontaneously resolve, and therefore, surgical or nonsurgical (e.g., mannitol, glucocorticoids) treatment may be necessary.

Prognosis and CT

There is a significant need for objective measures to predict the clinical course of TBI patients. Clinical variables, including GCS scores, extent of amnesia, duration of ventilatory support, and duration of intensive care unit stay, have weak relationships with subsequent neuropsychiatric testing.[101] Although some anatomic imaging findings such as the presence of blood or subarachnoid hemorrhage, intraventricular hemorrhage, edema, midline shift, effacement of the basal cisterns, and location of lesions have been found to be predictive of overall survival, they are not adequately predictive of functional outcome, even when clinical data are added.[102–106]

Ultimately, functional outcome depends on how many neurons are preserved after injury. However, the location of damage and the ability of existing neurons to reorganize their connections to recover function are also critical. Neuronal injury is caused by direct injury, compression, ischemia, and diffuse axonal injury (DAI). DAI, which occurs in up to 48% of patients with closed head injuries, is caused by the shear force generated by the rapid deceleration in motor vehicle accidents.[60] The force may either tear the axons or alter axoplasmic membranes, which subsequently impairs axoplasmic transport and results in delayed damage to axons. DAI usually is diffuse and bilateral, frequently involves the lobar white matter at the gray-white matter interface and may be

reversible. Although DAI is rarely fatal, it can result in significant neurological impairment. The number of lesions correlates with poorer outcomes, and lesions in the supratentorial white matter, corpus callosum, and corona radiate correlate with a greater likelihood that the patient will remain in a persistent vegetative state. Whereas hemorrhagic axonal injury can be seen on CT as multiple foci of high attenuation, nonhemorrhagic injury can be missed. In fact, CT is abnormal in less than half of all patients with DAI.[52,107]

Prognosis and MRI

MRI is generally more sensitive than CT for detecting neuronal damage. Patients with widespread MRI abnormalities or brain stem injuries usually show no significant neurological recovery, even when they have normal CT scans and intracranial pressures. However, aside from such obvious cases of devastating injury, a consistent relationship between MRI lesions and clinical or neuropsychological outcomes has not been demonstrated.[108,109]

Various newer MR technologies may provide better information for prognosis and rehabilitation guidance. Investigators have used MTI to detect white matter abnormalities in multiple sclerosis, progressive multifocal leukoencephalopathy, and Wallerian degeneration. Through MTI, a magnetization transfer ratio can be derived and quantitatively measure the structural integrity of tissues. MTI changes have been found to be more sensitive than T2-weighted MRI in detecting histologic axonal damage in animal models.[110,111] Bagley and colleagues[112] found associations between MTI abnormalities and neurological deficits.

Proton MR spectroscopy can detect the amount of creatinine, choline, myo-inositol, and N-acetylaspartate (NAA) in a selected tissue volume.[113] NAA, whose function has not been clearly established, has been found to be a marker for neuronal loss in a wide variety of conditions including spinal cord injury, amyotrophic lateral sclerosis, Parkinson disease, Huntington disease, ischemic stroke, progressive multifocal leukoencephalopathy, epilepsy, and multiple sclerosis, as reviewed separately in the current volume.[5,113] Animal models of brain injury have shown NAA levels to decrease within hours after injury.[5,114,115] Several investigators have found lower NAA to creatinine ratios as measured by MR spectroscopy to correlate with poorer clinical outcomes.[58,116,117] Finally, functional MRI studies by McAllister and colleagues[59] found persistent changes in the brain activation patterns of mild TBI patients compared with controls when given various working memory tasks.

Prognosis and SPECT

SPECT can detect abnormalities in cerebral blood flow (CBF) as reviewed separately in the current volume.[118] Not all alterations in cerebral blood flow are associated
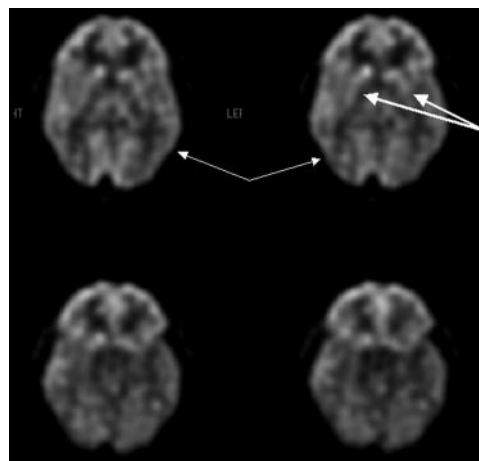

FIG. 5. FDG-PET scan of 33-year-old male status post motor vehicle accident demonstrates hypometabolism affecting the temporo-parietal and occipital (thin arrows) regions as well as the caudate and putamen (thick arrows), which are findings suggesting diffuse axonal injury.

with lesions on CT and *vice versa*.[119,120] In general, SPECT is more sensitive than CT in detecting lesions in TBI patients.[121,122] However, it is not always clear whether the abnormalities observed on SPECT correspond to direct or indirect injury, or possibly abnormalities from prior trauma or other neuropsychiatric conditions. CBF abnormalities are commonly seen in mild TBI patients with chronic symptoms, even if no structural damage is apparent.[123] Often the size of the lesion on SPECT exceeds the size of the lesion on CT or MRI.

SPECT appears to be better than CT or MRI in determining long-term prognosis.[122,124] A negative initial SPECT scan after trauma seems to strongly predict a favorable clinical outcome.[125] A worse prognosis is associated with larger lesions, multiple defects, and lesions in the brainstem, temporal lobes, parietal lobes, or basal ganglia. Abnormal SPECT can be predictive of neuropsychological deficits.[126] Studies have found that decreased blood flow to various parts of the brain correlate with various types of behavior: the frontal lobes with disinhibitive behavior, the left cerebral hemisphere with increased social isolation, and the right hemispheric areas with increased aggressive behavior.[127] Deficits in frontal lobe and thalamic perfusion have been linked to impairments in executive functioning.[128] However, no consistent correlation between SPECT abnormalities and neuropsychological test scores has been established.[129] Because MRI detects lesions missed by SPECT and *vice versa*, a combination of MR and SPECT may be even better for determining prognosis.[130]

Prognosis and PET

As reviewed separately in the current volume,[131] PET measures the cerebral metabolism of various substrates, most commonly fluorodeoxyglucose in the measurement of glucose metabolism, which should correspond to neu-
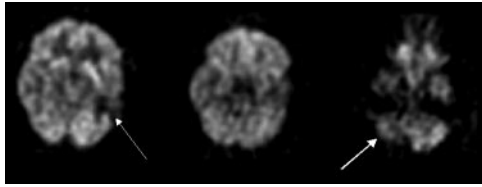
FIG. 6. FDG-PET scan of a 38-year-old male with head injury 15 years ago with encephalomalacia in the left temporal lobe demonstrates marked hypometabolism in the left temporal lobe (thin arrow) and right cerebellar hypometabolism (thick arrow) consistent with crossed cerebellar diaschisis.

ronal viability. PET can also be used to diagnose patients with DAI to determine the extent of damage and prognosis (FIG. 5). PET studies may help delineate reversible and irreversible lesions to direct therapeutic interventions toward preventing further damage. The major limitation of PET imaging is that it cannot distinguish between functional abnormalities associated and not associated with structural damage. In general, studies have found that cerebral dysfunction can extend far beyond the boundary of anatomical lesions and may even appear in locations remote from the trauma. Alavi and colleagues[132] showed that approximately 33% of anatomical lesions were associated with larger and more widespread metabolic abnormalities. As much as 42% of PET abnormalities were not associated with any anatomical lesions observed on anatomical images. The metabolic effects of cortical contusions, intracranial hematoma, and resultant encephalomalacia are primarily confined to the site of injury (FIG. 6), whereas those of subdural and epidural hematomas often are widespread and may even affect the contralateral hemisphere. DAI results in diffuse hypometabolism.[132,133]

Alavi and colleagues[132] found that GCS scores of 13 and lower were associated with whole brain hypometabolism on ^{18}F-fluorodeoxyglucose (FDG)-PET. Studies have shown that PET can uncover areas of cerebral hypometabolism that are associated with neurological and behavioral dysfunction but not detected on CT, MRI, or EEG (FIGS. 7 and 8).[134,135] Moreover, some of these areas eventually develop structural abnormalities such as encephalomalacia and atrophy on CT. Separate studies by Gross[136] and Ruff[137] found PET hypometabolism to significantly correlate with overall clinical complaints and overall neuropsychological test results. However,
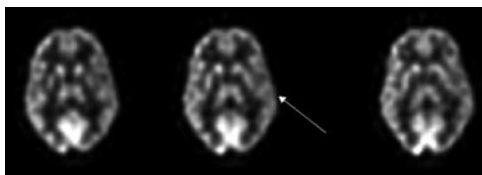

FIG. 7. FDG-PET scan of a 43-year-old female with head injury 2 years ago now with cognitive and memory dysfunction as well as language problems demonstrates hypometabolism in the entire left hemisphere (arrow) related to the head trauma.
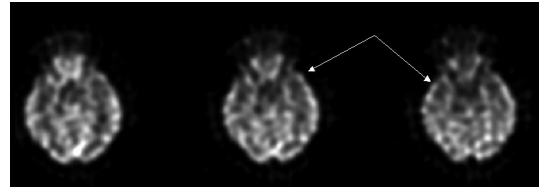

FIG. 8. FDG-PET scan of a 49-year-old female with MVA 6 years ago and persistent headache and memory problems with bilateral decreased temporal lobe metabolism (arrows).

PET imaging can also uncover other potentially confounding neuropsychiatric conditions such as depression or drug induced effects (FIG. 9). Furthermore, several studies have shown that the glucose metabolic abnormalities observed on PET are associated with a number of possible mechanisms and therefore may not provide sufficient data to assess global function and level of consciousness in head injury patients.[138,139]

Imaging and new therapies

Imaging is playing a crucial role in defining the mechanisms of secondary injury in TBI and, in turn, potentially identifying targets of new therapies.[140] TBI is found to initiate an inflammatory cascade that results in the release of amino acids, such as glutamate and aspartate, and free radicals, that may lead to further tissue damage.[141] Other potential culprits include nitrous oxide, endogenous opioid peptides such as naloxone, catecholamines, acetylcholine, thyrotropin-releasing hormone (TRH), lactate, and adenosine.[142,143] Cytokines such as tumor necrosis factor (TNF) and interleukins 1,6, and 8, also have found to increase following TBI.[144,145] PET, functional MRI, MR spectroscopy, and SPECT, have been and will continue to be crucial in identifying the concentrations and locations of these various molecules in animal and human brains following injury. In animal models, imaging has been used to determine the effectiveness of glutamate and *N*-methyl-D-aspartate receptor blockers and antioxidants on TBI.[146,147] Ischemia and reperfusion injury are thought to play important roles, and imaging has been important in understanding perfusion changes after TBI as well helping develop therapies to alter perfusion.[148,149] Using PET to measure CBF, oxygen metabolism, and the oxygen extraction
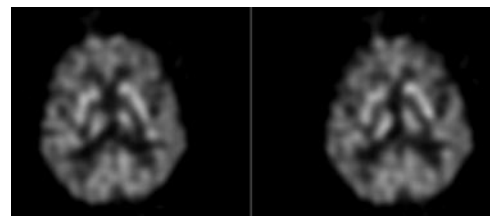

FIG. 9. FDG-PET scan of a 69-year-old boxer with visual and memory problems evaluated for dementia pugilistica. The findings demonstrate moderate global cortical hypometabolism and preservation of subcortical and occipital structures most consistent with depression, not DAI.

fraction (OEF) in severe brain injury, Yamaki and colleagues[150] found that long-lasting anaerobic glycolysis with high OEF and a relatively low ratio of oxygen metabolism to glucose metabolism predicted poor outcomes. SPECT and PET imaging have been used to measure improvements in cerebral blood flow associated with hyperbaric oxygen therapy[151] and hyperventilation[152] therapy in TBI patients.

CONCLUSIONS

In the future, the already significant role of imaging in guiding therapy may grow. Technological improvements continue to reduce scanning time and improve resolution. New methods are being developed to quantify damage on images and perhaps improve predictive power. A growing number of minimally invasive, image-guided techniques are replacing open surgical techniques. Imaging is increasingly vital to the development of new therapies and may be used to measure patient response to these therapies. Imaging has and will continue to influence therapy and may improve outcomes for what is clearly a significant health care problem.

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